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Review Article

Meta-analysis of pregabalin combined with different methods for treating postherpetic neuralgia

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Abstract: Objective: To conduct a meta-analysis of the literature on the treatment of postherpetic neuralgia (PHN) with pregabalin combined with different methods. Methods: Search for relevant literature on the treatment of postherpetic neuralgia with pregabalin combined with different methods in both Chinese and English databases, including PubMed, Web of science, Cochrane Library, Wanfang Data, and China National Knowledge Infrastructure (CNKI). Results: The final inclusion consisted of 29 articles published between 2009 and 2023, with a total of 2,738 patients. Among them, 22 articles were RCTs, and 7 were non-RCTs. Seven articles reported on NRS, and the meta-analysis of continuous variable showed that the NRS scores in the study group were significantly lower than in the control group (OR = -1.05, 95% CI: -1.37 to -0.73, Z = -6.47, P < 0.01). Seven articles reported on breakthrough pain, and the meta-analysis of continuous variable showed that the frequency of breakthrough pain in the study group was significantly lower than in the control group (OR = -1.23, 95% CI: -1.52 to -0.94, Z = -8.31, P < 0.01). Five articles reported on SF-MPQ, and the meta-analysis of continuous variable showed that the SF-MPQ in the study group was significantly lower than in the control group (OR = -1.47, 95% CI: -2.14 to -0.81, Z = -4.33, P < 0.01). Ten articles reported on sleep quality, and the meta-analysis of continuous variable showed that the sleep quality scores in the study group were significantly lower than in the control group (OR = -2.16, 95% CI: -3.46 to -0.86, Z = -3.26, P < 0.01). Twenty articles reported on VAS, and the meta-analysis of continuous variable showed that the VAS scores in the study group were significantly lower than in the control group (OR = -1.17, 95% CI: -1.49 to -0.85, Z = -7.15, P < 0.01). Seven articles reported on efficacy, and the meta-analysis of dichotomous variable showed that the efficacy in the study group was significantly higher than in the control group (OR = 1.45, 95% CI: 0.94 to 1.95, Z = 5.65, P < 0.01). Thirteen articles reported on adverse reactions, and the meta-analysis of dichotomous variable showed no statistically significant difference in adverse reactions between the study and control groups (OR = 0.31, 95% CI: -0.01 to 0.62, Z = 1.92, P = 0.06). Ten articles reported on quality of life, and the meta-analysis of continuous variable showed that the quality of life scores in the study group were significantly higher than in the control group (OR = 1.00, 95% CI: 0.73 to 1.27, Z = 7.20, P < 0.01). Eleven articles reported on pregabalin dosage, and the meta-analysis of continuous variable showed that the dosage of pregabalin in the study group was significantly lower than in the control group (OR = -2.55, 95% CI: -3.15 to -1.95, Z = -8.30, P < 0.01). Funnel plot analysis indicated publication bias in VAS and pregabalin dosage but no publication bias in adverse reactions. Conclusion: Pregabalin combined with electroacupuncture, medications, pulsed radiofrequency, and nerve stimulation has shown good efficacy in the treatment of PHN and can be flexibly applied based on clinical practice.

Keywords: Pregabalin, PHN, VAS, adverse reactions, meta-analysis

Introduction

Postherpetic neuralgia (PHN) is a common neurological disorder primarily caused by the reactivation of the Varicella zoster virus (VZV) latent in the nerve root ganglia, leading to acute pain, chronic pain, hyperalgesia, and numbness, among other symptoms [1]. Depending on the extent of nervous system damage, PHN can be categorized into irritable nociceptor group, deafferentation group, central reorganization group, and non-irritable nociceptor group. As the severity of pain increases, patients may also experience severe emotional disturbances and mental health issues [2]. This condition mostly affects the thoracic and facial areas, and during episodes, the herpes zoster region may exhibit pain along with sensations of burn-

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ing and tightness. Clinical treatments include calcium channel modulators, antiviral agents, pulsed radiofrequency, and electrical nerve stimulation, among other methods [3]. Pregabalin, in particular, effectively blocks voltage-dependent calcium channels, reducing neurotransmitter release and thus alleviating neuropathic pain or muscle pain, lowering serum inflammation levels, and modulating immune system function [4]. Ling DY et al. [5] pointed out that pregabalin combined with dorsal root ganglion pulsed radiofrequency therapy can significantly improve the sleep quality and physical and mental comfort of PHN patients, thereby reducing the dosage of other opioid analgesics. Kopel J et al. [6] found that pregabalin not only improves efficacy but can also serve as a first-line therapy for PHN and other neuropathic pain, especially when gabapentin treatment fails. Xu J et al. [7] demonstrated that combining pulsed radiofrequency with pregabalin significantly enhances analgesic effects and reduces the daily dosage of tramadol and pregabalin. Therefore, in addition to rapid pain relief, it is essential to avoid relying solely on medication and adopt targeted comprehensive treatments based on the primary and secondary injury-affected nerve innervation regions. This paper conducts a search and meta-analysis of literature in Chinese and English databases on the treatment of PHN with pregabalin combined with different methods, providing insights for optimizing clinical combination therapy for PHN and reducing the treatment burden on patients.

Materials and methods

Data sources

Using a computer, we searched Chinese and English databases for literature related to the treatment of PHN with pregabalin combined with different methods, covering the period from January 2000 to May 2024. In the Chinese databases, including Wanfang Med Online, China National Knowledge Infrastructure (CNKI), Chinese Medical Association, and National Science and Technology Library, we used the search terms: pregabalin, herpes zoster, postherpetic neuralgia, pregabalin combined with radiofrequency pulse, pregabalin combined with electrical nerve stimulation, and traditional Chinese medicine combined with pregabalin. In the English databases, including PubMed, Web of Science, Wiley InterScience, Cochrane Library, and Springer Link, we used the search terms: pregabalin, PHN, herpes zoster, pregabalin united, radio-frequency pulse, nerve regeneration, and pregabalin combined with electrical nerve stimulation.

Literature screening

Inclusion criteria: ① Literature published between January 2000 and May 2024; ② Study subjects diagnosed with PHN based on herpes history, clinical symptoms, rash characteristics, and blood biochemistry tests [8]; ③ Study subjects had not used sedatives, hypnotics, or stimulants affecting the nervous system within 2 weeks before treatment; ④ Study subjects had no history of peripheral or central nervous system surgery; ⑤ The literature focused on the treatment of PHN with pregabalin combined with other methods (including Western medicine, traditional Chinese medicine, physical therapies, etc.).

Exclusion criteria: ① Reports, quantitative analyses, descriptive studies, case studies, theoretical reviews, personal experience summaries, animal experiments, or meta-analyses related to PHN or pregabalin; ② Study subjects with concurrent viral infections or neuropathic pain; ③ Studies focused on the economic benefits of drugs; ④ Unpublished works or those with academic copyright disputes; ⑤ Incomplete information, such as unclear authorship, ambiguous research methods, inability to access the full text, missing volume or issue numbers, and lack of abstracts or keywords.

Duplicate checking and data extraction

Import the titles of the literature retrieved from Chinese and English databases into the NoteExpress 3.2 document retrieval and management system. After deduplication, review the titles and abstracts to exclude studies with poor quality or relevance. Then, two researchers independently screen the literature according to the inclusion and exclusion criteria and extract the information. In case of disputes, invite a third party with more clinical experience or higher professional qualifications for judgment. The literature information includes: ① Basic information such as the first author, pub-

lication year, journal, and country; ② Basic data on study subjects, including source, gender, age, number, and disease duration; ③ Study type, grouping methods, research content and objectives, intervention methods, outcome measures/observational indicators, and study results; ④ Key factors affecting bias risk assessment.

Bias risk assessment

Use the 'Risk of Bias Assessment Tool' in Cochrane's Review Manager 5.4 to evaluate the quality of the finally included literature. The evaluation includes: ① Grouping methods; ② Allocation concealment; ③ Blinding, including whether patients, researchers, and outcome assessors were blinded; ④ Data integrity; ⑤ Selective reporting of study results; ⑥ Other sources of bias, such as inauthentic research data, research targeting a specific population, or falsified research statements. The levels of bias risk are: low risk, high risk, and unclear risk. After evaluation, summarize the results and use the built-in functions of Review Manager 5.4 to create a risk of bias chart.

Statistical analysis

Use the meta module in Stata 18.0 for data analysis. For dichotomous variables, effect measures are reported as odds ratios (OR) with 95% confidence intervals (CI). For continuous variables, effect measures are reported as mean differences (MD) with 95% CI. If the units of continuous variable data differ among studies, the effect sizes will beare expressed as standardized mean differences (SMD) with 95% CI. Heterogeneity is assessed using the Q-test and quantified with I^2. If there is no statistically significant heterogeneity among study results ($P > 0.1$, $I^2 \leq 50\%$), a fixed-effect model is used to calculate the combined OR and 95% CI. If there is statistically significant heterogeneity among study results ($P \leq 0.1$, $I^2 > 50\%$), a random-effects model is used to calculate the combined OR and 95% CI. Forest plots are created, and funnel plot analysis is conducted for combined results with more than 10 studies to assess publication bias. Additionally, Z-tests are performed on the combined OR values and 95% CI, with $P < 0.05$ indicating statistical significance of the combined statistics from multiple studies.

Results

Literature search and process

After searching databases using Chinese and English keywords, a total of 4,271 relevant articles on 'Pregabalin Combined with Different Methods for Treating PHN' were identified. An additional 7 relevant articles were obtained from other resources. The titles of these articles were imported into the NoteExpress 3.2 document retrieval and management system for deduplication, removing 3,219 articles, leaving 1,059 articles. Titles and abstracts were then reviewed, and 754 articles with lower relevance or quality were excluded, leaving 305 articles. Based on the inclusion and exclusion criteria, an additional 282 articles were excluded. Ultimately, 29 articles [9-37] were included, with 7 [16-19, 23, 36, 37] in Chinese and 22 [9-15, 24-35] in English. The literature search process is shown in **Figure 1**.

Key information of included studies

Among the 29 articles finally included, published between 2009 and 2023, a total of 2,738 patients were involved. Of these, 22 articles [9, 11-18, 20, 23, 25, 27-32, 34-37] were RCTs, and 7 articles [10, 19, 21, 22, 24, 26, 33] were non-RCTs. Details are provided in **Table 1**.

Bias risk assessment of included studies

Among the 29 included articles, 22 [9, 11-16, 20, 23-32, 34-37] were grouped using random number tables or random odd-even methods and were all rated as 'low risk'; 3 articles [10, 17, 22] were grouped by treatment methods, and 2 articles [18, 21] did not specify the grouping methods, all rated as 'unclear risk'; 1 article [19] was grouped by order of visit, and 1 article [33] was grouped by treatment methods, both rated as 'high risk'. Four articles [11, 12, 14, 25] had allocation concealment and were rated as 'low risk'; 25 articles [9, 10, 13, 15-24, 26-37] did not describe allocation concealment and were rated as 'unclear risk'. Five articles [10-12, 14, 25] used double blinding and were rated as 'low risk'; 24 articles [9, 13, 15-24, 26-37] did not describe double blinding settings and were rated as 'unclear risk'. All 29 articles had complete research data, with no selective reporting, reporting bias, or other

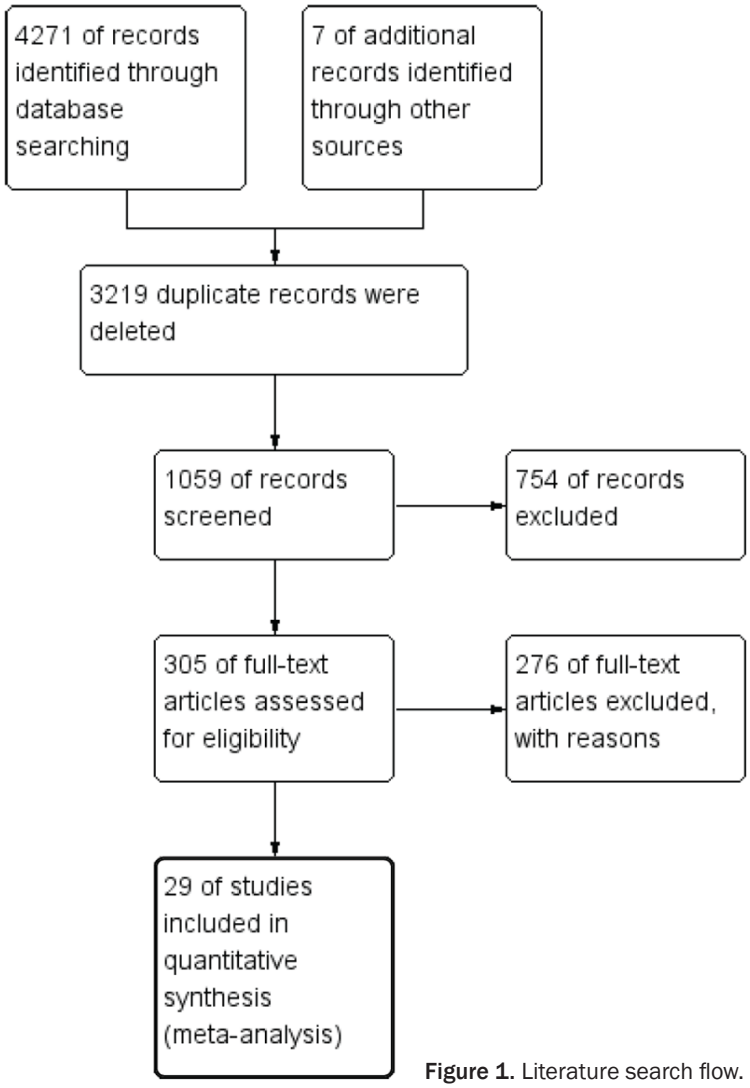

Figure 1. Literature search flow.

biases, and were all rated as 'low risk', as shown in **Figure 2**.

Meta-analysis of major outcomes

Meta-analysis of NRS: Seven articles [9, 20, 22, 30, 32, 36, 37] reported on NRS, including 14 groups and 1,015 patients. A meta-analysis was conducted using NRS scores as a continuous variable. There was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the NRS scores in the intervention group were significantly lower than those in the control group (OR = -1.05, 95% CI: -1.37 to -0.73, Z = -6.47, P < 0.01). The NRS scores in six subgroups, including 'Pregabalin + EA', 'Pregabalin + PNS', and 'Pregabalin + hydromorphone', were significantly lower than those in the control group (all P < 0.01), as shown in **Figure 3**.

Meta-analysis of breakthrough pain: Seven articles [9, 19, 26-30] reported on breakthrough pain, including 14 groups and 966 patients. A meta-analysis was conducted using pain frequency as a continuous variable. There was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the frequency of breakthrough pain in the intervention group was significantly lower than that in the control group (OR = -1.23, 95% CI: -1.52 to -0.94, Z = -8.31, P < 0.01). The frequency of breakthrough pain in seven subgroups, including 'Pregabalin + Acyclovir + Ropivacaine + Methylprednisolone', 'Pregabalin + EA', and 'Pregabalin + Valaciclovir + Methylprednisolone', was significantly lower than that in the control group (all P < 0.01), as shown in **Figure 4**.

Meta-analysis of SF-MPQ: Five articles [9, 13-15, 30] reported on SF-MPQ, including 10 groups and 839 patients. A meta-analysis was conducted using SF-MPQ scores as a continuous variable. There was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the SF-MPQ scores in the intervention group were significantly lower than those in the control group (OR = -1.47, 95% CI: -2.14 to -0.81, Z = -4.33, P < 0.01). The SF-MPQ scores in five subgroups, including 'Pregabalin + EA', 'Pregabalin + TENS', and 'Pregabalin + hydromorphone', were significantly lower than those in the control group (all P < 0.05), as shown in **Figure 5**.

Meta-analysis of sleep quality scores: Ten articles [9, 10, 13, 14, 17, 18, 20, 31, 33, 37] reported on sleep quality, including 20 groups

Table 1. Key information of included studies

Author	Year	n	Type	Research group	Control group	Research measure	Control measure	Observation index
Huang Y et al. [9]	2021	201	RCT	101	100	Pregabalin + hydromorphone	Pregabalin + NaCl	①②③④
Li HQ et al. [10]	2023	103	Non RCT	52	51	Pregabalin + HL-PRF	Pregabalin	④⑤⑥⑦⑧
Saxena AK et al. [11]	2016	60	RCT	30	30	Pregabalin + PRF	Pregabalin	⑤
Makharita MY et al. [12]	2018	156	RCT	78	78	Pregabalin + PRF	Pregabalin	⑤⑨
Barbarisi M et al. [13]	2010	30	RCT	15	15	Pregabalin + TENS	Pregabalin	③④⑤
Zin CS et al. [14]	2010	62	RCT	31	31	Pregabalin + oxycodone	Pregabalin	③④⑤
Hu B et al. [15]	2018	98	RCT	49	49	Pregabalin + ozone autohemotherapy	Pregabalin	③⑤⑨⑩
Wang WJ et al. [16]	2013	77	RCT	41	36	Pregabalin + EA	Pregabalin	⑤⑦
Huang RS et al. [17]	2013	44	RCT	22	22	Pregabalin + Nerve block	Pregabalin	④⑤⑧
Qu YX et al. [18]	2022	72	RCT	36	36	Pregabalin + self-prepared Huayu Zhitong Decoction	Pregabalin	④⑤⑦⑧
Yang J et al. [19]	2014	64	Non RCT	32	32	Pregabalin + prednisone	Pregabalin	②⑤⑧⑪
Cao Y et al. [20]	2019	60	RCT	30	30	Pregabalin + spinae plane block	Pregabalin	①④⑦⑧⑫
Makharita MY et al. [21]	2012	61	Non RCT	30	31	Pregabalin + Conventional + early stellate ganglion blockade	Pregabalin + Conventional	⑤⑫
Baron R et al. [22]	2009	128	Non RCT	57	71	Pregabalin + lidocaine medicated plaster	Lidocaine medicated plaster	①⑧⑩
Chen Y et al. [23]	2015	60	RCT	28	32	Pregabalin + Sertraline	Pregabalin	⑤⑧⑨
Wan CF et al. [24]	2022	120	Non RCT	60	60	Pregabalin + HL-PRF	Pregabalin + PRF	⑤⑧⑨⑫
Wan C et al. [25]	2019	96	RCT	48	48	Pregabalin + PRF	Pregabalin	⑤⑧⑨⑫
Dong DS et al. [26]	2017	46	Non RCT	24	22	Pregabalin + stSCS	Pregabalin	②⑤⑨⑫
Cui JZ et al. [27]	2018	97	RCT	49	48	Pregabalin + Acyclovir + ropivacaine + Methylprednisolone	Pregabalin + Acyclovir + NaCl	②⑫
Choudhary S et al. [28]	2018	30	RCT	15	15	Pregabalin + Valaciclovir + Methylprednisolone	Pregabalin + Valaciclovir	②⑤
Makharita MY et al. [29]	2020	80	RCT	40	40	Pregabalin + bupivacaine + Dexamethasone	Pregabalin + bupivacaine + Dexamethasone	②⑫
Liu Q et al. [30]	2021	448	RCT	224	224	Pregabalin + EA	Pregabalin	①②③⑧⑩⑪
Sun R et al. [31]	2022	88	RCT	44	44	Pregabalin + EA	Pregabalin	④⑤⑧⑨⑪
Fan X et al. [32]	2022	75	RCT	38	37	Pregabalin + PNS	Pregabalin	①⑧⑨⑫
Huang M et al. [33]	2022	160	Non RCT	109	51	Pregabalin + stSCS	Pregabalin + tSNRS	⑤④⑨⑫
Liu DY et al. [34]	2021	52	RCT	26	26	Pregabalin + PNS	Pregabalin	⑤⑫
Sheng L et al. [35]	2022	70	RCT	35	35	Pregabalin + stSCS	Pregabalin + PRF	⑤⑦⑨⑫
Zhang ZY et al. [36]	2019	63	RCT	31	32	Pregabalin + stSCS	Pregabalin + PRF	①⑦
Li Fubo et al. [37]	2022	40	RCT	20	20	Pregabalin + stSCS	Pregabalin + PRF	①④⑦⑧

Notes: RCT: Randomized Controlled Trial; HL-PRF: High-Voltage Pulsed Radio Frequency; NaCl: Normal Saline; PRF: Pulsed Radio Frequency; TENS: Transcutaneous Electrical Nerve Stimulation; stSCS: Short-Term Spinal Cord Stimulation; tSNRS: Temporary Spinal Nerve Root Stimulation; EA: Electroacupuncture. ① Numeric Rating Scale (NRS); ② Breakthrough Pain; ③ Short-Form McGill Pain Questionnaire (SF-MPQ); ④ Sleep Quality Scores [Pittsburgh Sleep Quality Index (PSQI), Sleep Quality Rating]; ⑤ Visual Analogue Scale (VAS); ⑥ Inflammatory Markers (Serum Neuropeptide Y, Prostaglandin E2, Substance P, β-Endorphin, etc.); ⑦ Efficacy; ⑧ Adverse Reactions; ⑨ Quality of Life [MOS Item Short Form Health Survey (SF-36), World Health Organization Quality of Life (WHOQOL-BREF), etc.]; ⑩ Patient Global Impression of Change (PGIC) Scale; ⑪ Anxiety and Depression; ⑫ Pregabalin Dosage.

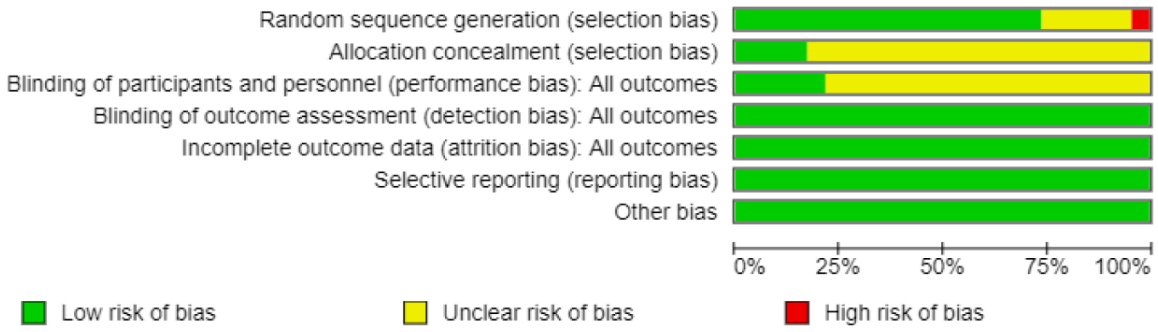

Figure 2. Summary of risk of bias in included studies.

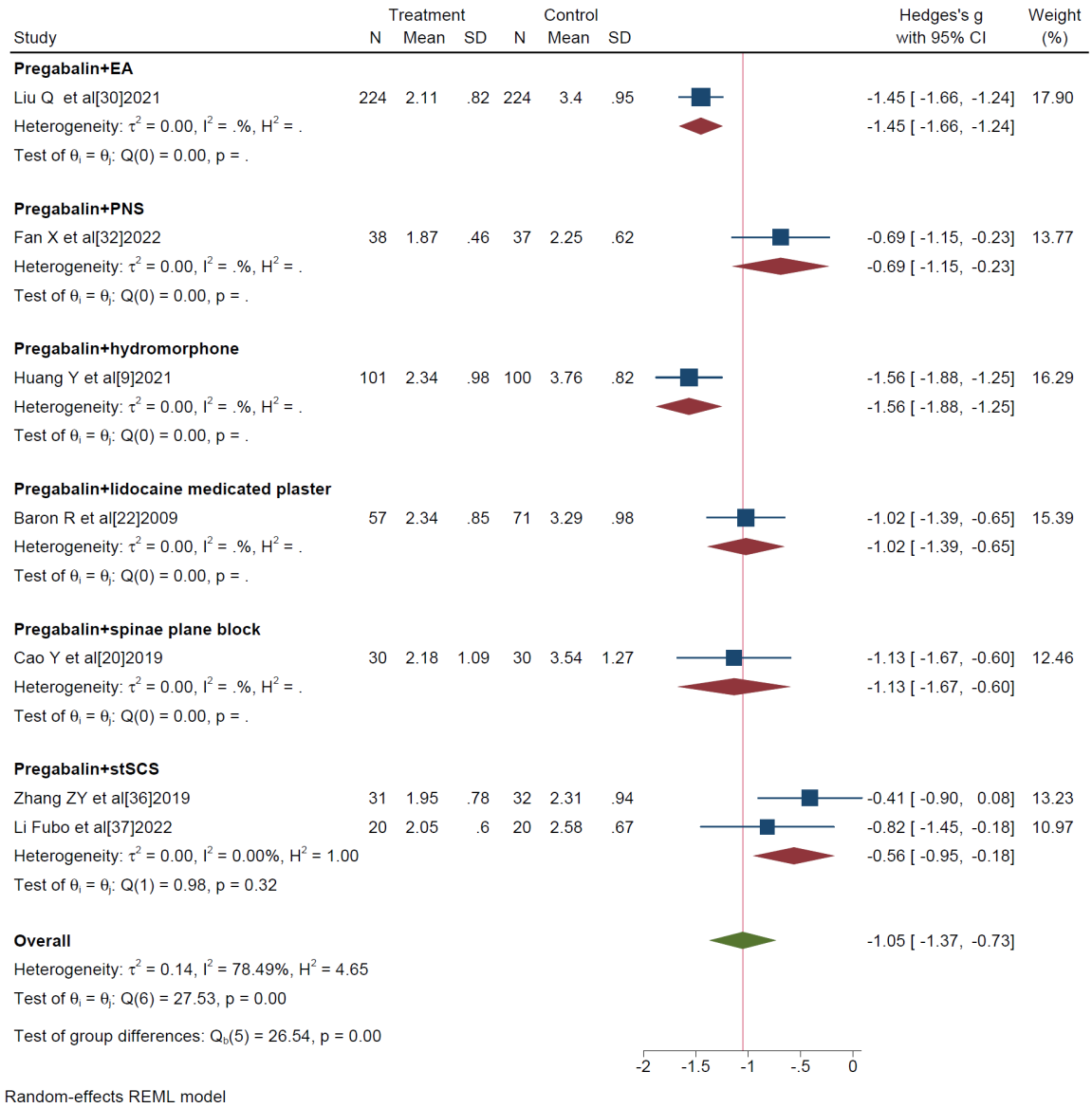

Figure 3. Meta-analysis of NRS.

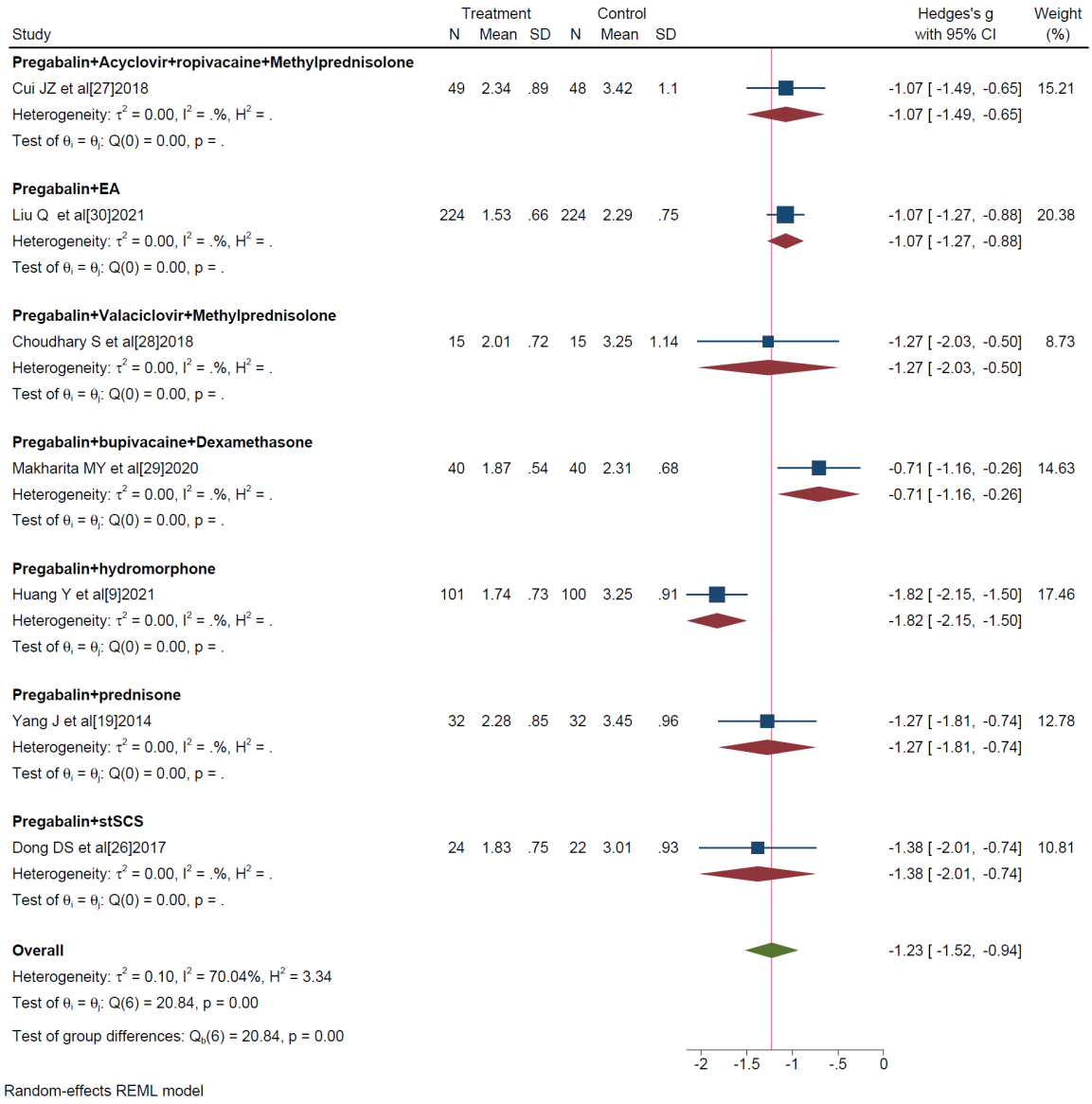

Figure 4. Meta-analysis of breakthrough pain.

and 860 patients. A meta-analysis was conducted using sleep quality scores as a continuous variable. There was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the sleep quality scores in the intervention group were significantly lower than those in the control group (OR = -2.16, 95% CI: -3.46 to -0.86, Z = -3.26, $P < 0.01$). The sleep quality scores in seven subgroups, including 'Pregabalin + EA', 'Pregabalin + HL-PRF', 'Pregabalin + Nerve block', 'Pregabalin + TENS', 'Pregabalin + hydromorphone', 'Pregabalin + self-prepared Huayu Zhitong Decoction', and 'Pregabalin + spinae plane block', were significantly lower than those in the control group (all $P < 0.05$); however, the sleep quality scores in the 'Pregabalin + oxycodone' and 'Pregabalin + stSCS' subgroups showed no significant difference compared to the control group ($P \geq 0.05$), as shown in **Figure 6**.

Meta-analysis of VAS: Twenty articles [10-26, 28, 31, 33-35] reported on VAS, including 40 groups and 1,545 patients. A meta-analysis was conducted using VAS scores as a continuous variable. There was significant heterogene-

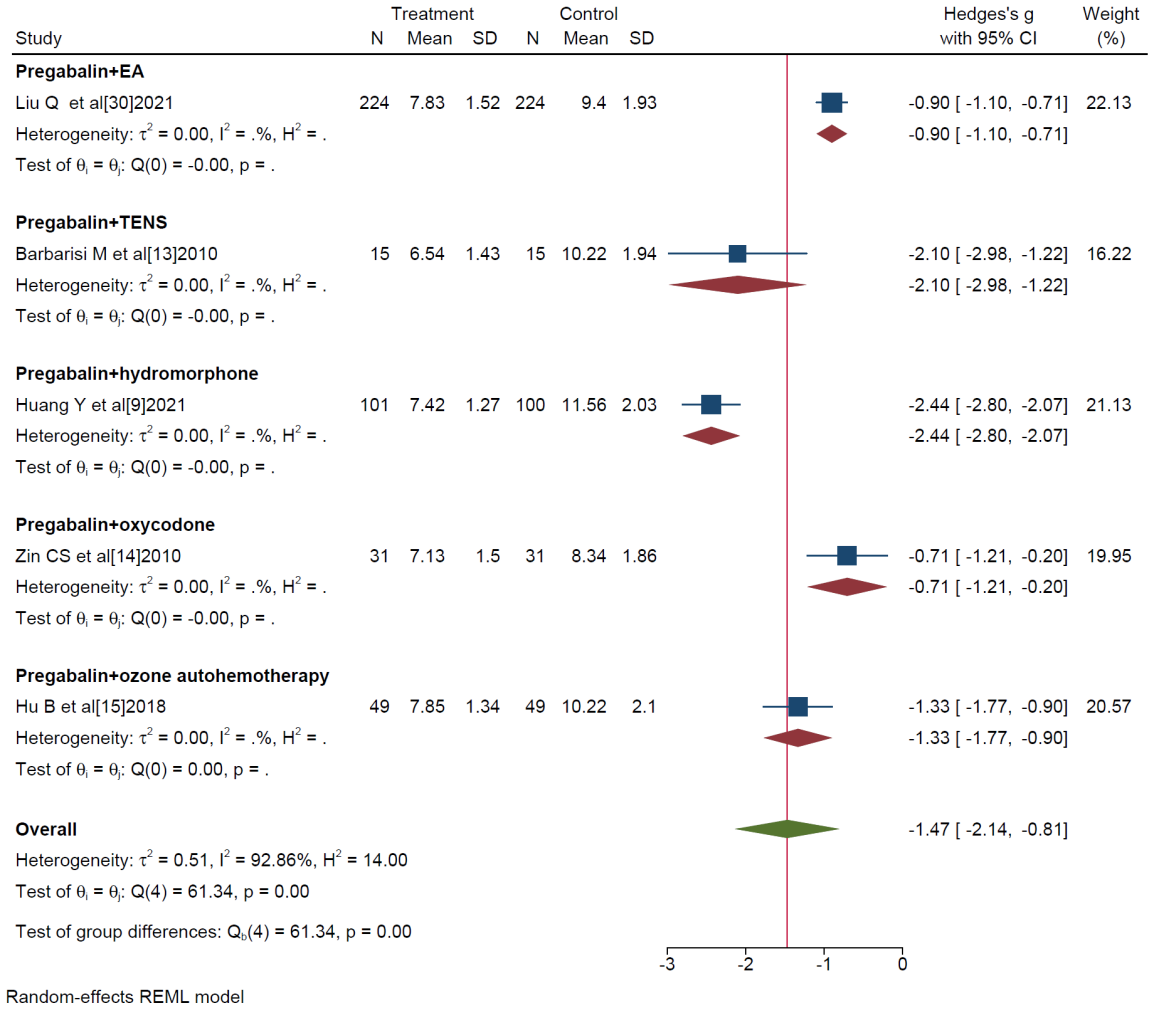

Figure 5. Meta-analysis of SF-MPQ.

ity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the VAS scores in the intervention group were significantly lower than those in the control group (OR = -1.17, 95% CI: -1.49 to -0.85, Z = -7.15, P < 0.01). The VAS scores in 12 subgroups, including 'Pregabalin + EA', 'Pregabalin + HL-PRF', 'Pregabalin + Nerve block', 'Pregabalin + PNS', 'Pregabalin + Sertraline', 'Pregabalin + TENS', 'Pregabalin + Valaciclovir + Methylprednisolone', 'Pregabalin + ozone autohemotherapy', 'Pregabalin + prednisone', 'Pregabalin + self-prepared Huayu Zhitong Decoction', 'Pregabalin + spinae plane block', and 'Pregabalin + stSCS', were significantly lower than those in the control group (all P < 0.05). However, the VAS scores in the 'Pregabalin + PRF' and 'Pregabalin + oxycodone' subgroups showed no significant difference compared to the control group (both $P \geq 0.05$), as shown in **Figure 7**.

Meta-analysis of efficacy: Seven articles [10, 16, 18, 20, 35-37] reported on efficacy, including 14 groups and 482 patients. A meta-analysis was conducted using total effective number as a dichotomous variable. No significant heterogeneity was observed among the study results (P > 0.1, I^2 < 50%), so a fixed-effect model was used for analysis. The results confirmed that the efficacy in the intervention group was significantly higher than that in the control group (OR = 1.45, 95% CI: 0.94 to 1.95, Z = 5.65, P < 0.01). The efficacy in the subgroups 'Pregabalin + EA', 'Pregabalin + self-prepared Huayu Zhitong Decoction', 'Pregabalin + spinae plane block', and 'Pregabalin + stSCS' was significantly higher than that in the control

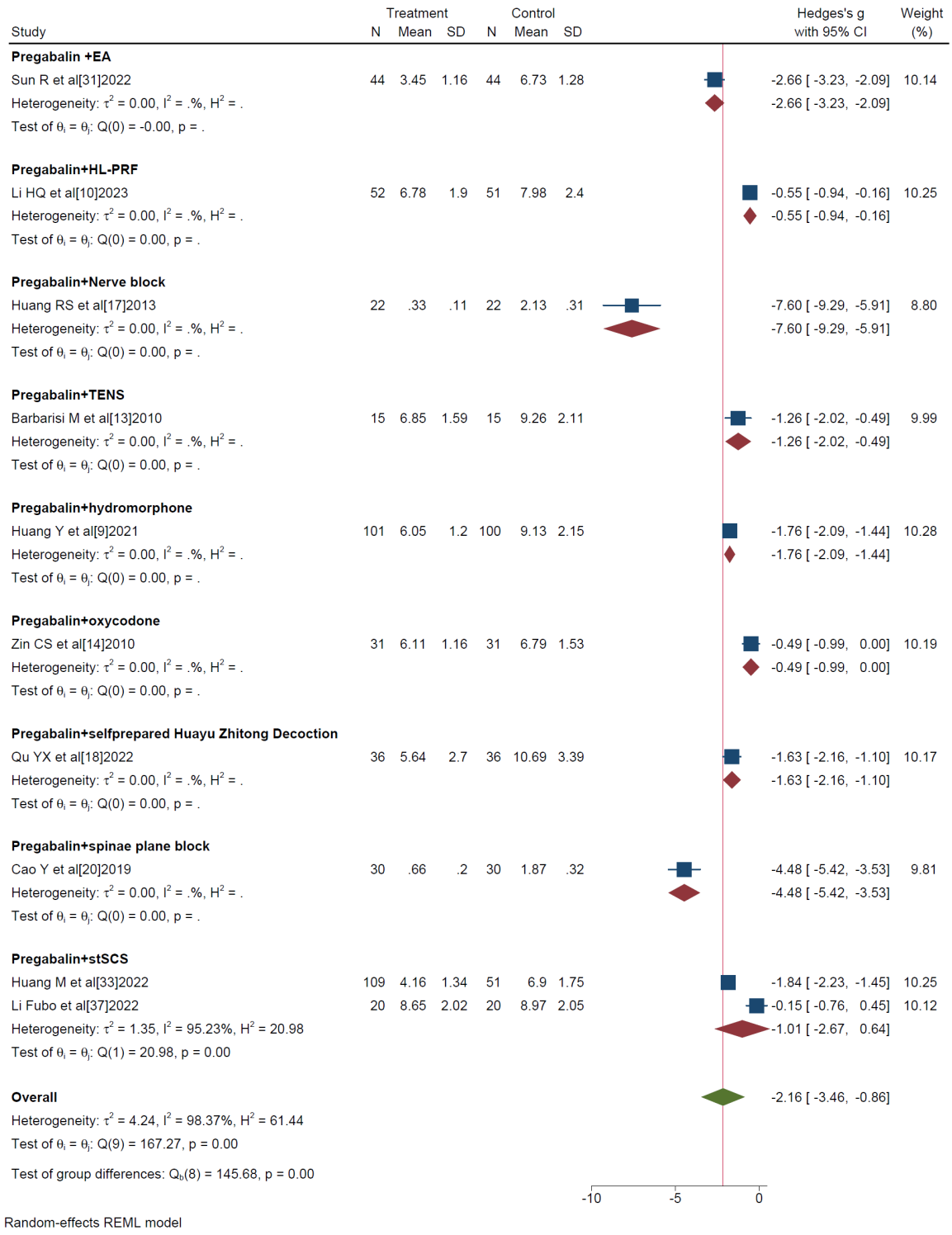

Figure 6. Meta-analysis of sleep quality scores.

group (all P < 0.05). However, the efficacy in the 'Pregabalin + HL-PRF' subgroup showed no significant difference compared to the control group (P > 0.05), as shown in **Figure 8**.

Meta-analysis of adverse reactions: Thirteen articles [10, 17-20, 22-25, 30-32, 37] reported on adverse reactions, including 26 groups and 1,398 patients. A meta-analysis was conduct-

Meta-analysis of pregabalin in the treatment of postherpetic neuralgia

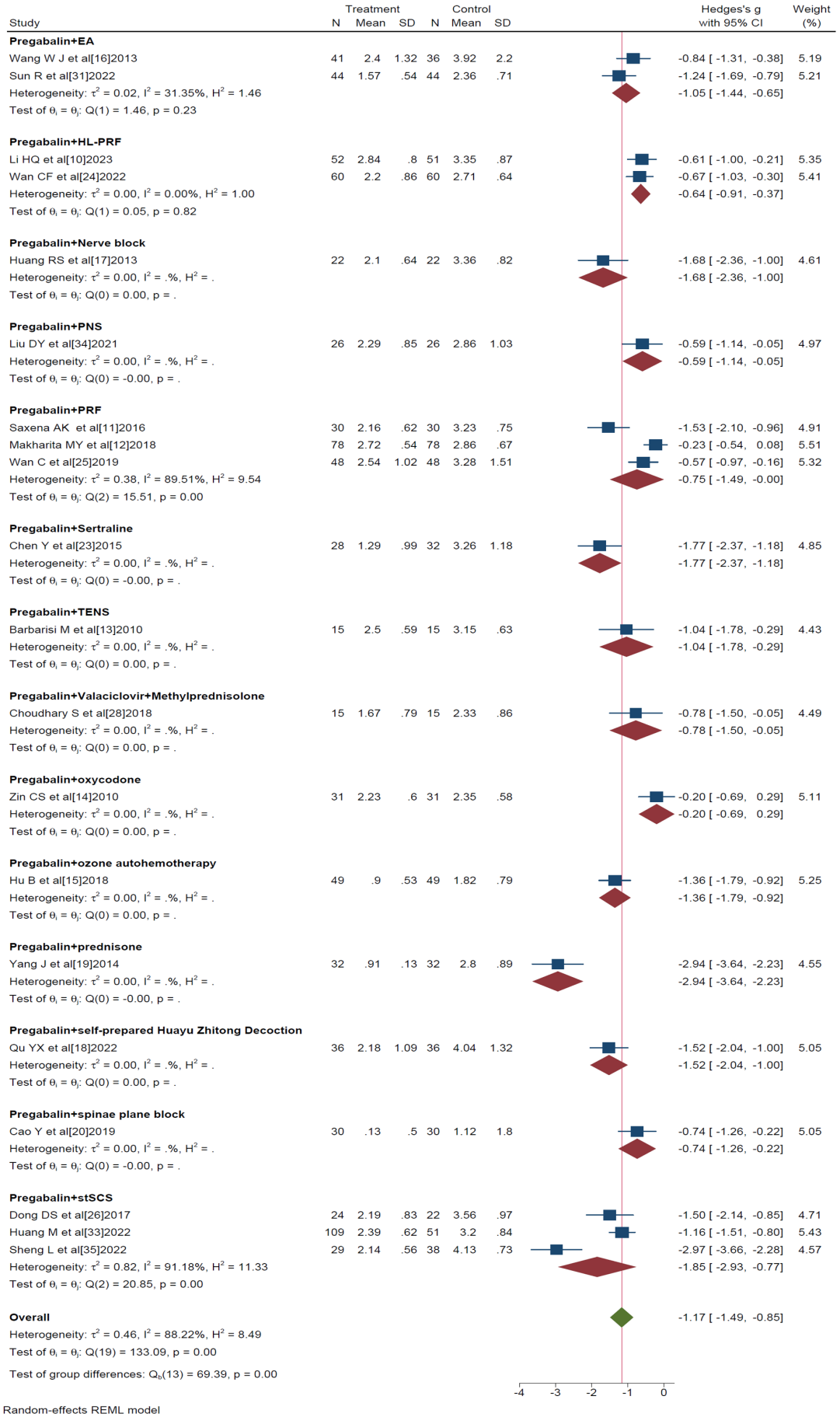

Figure 7. Meta-analysis of VAS.

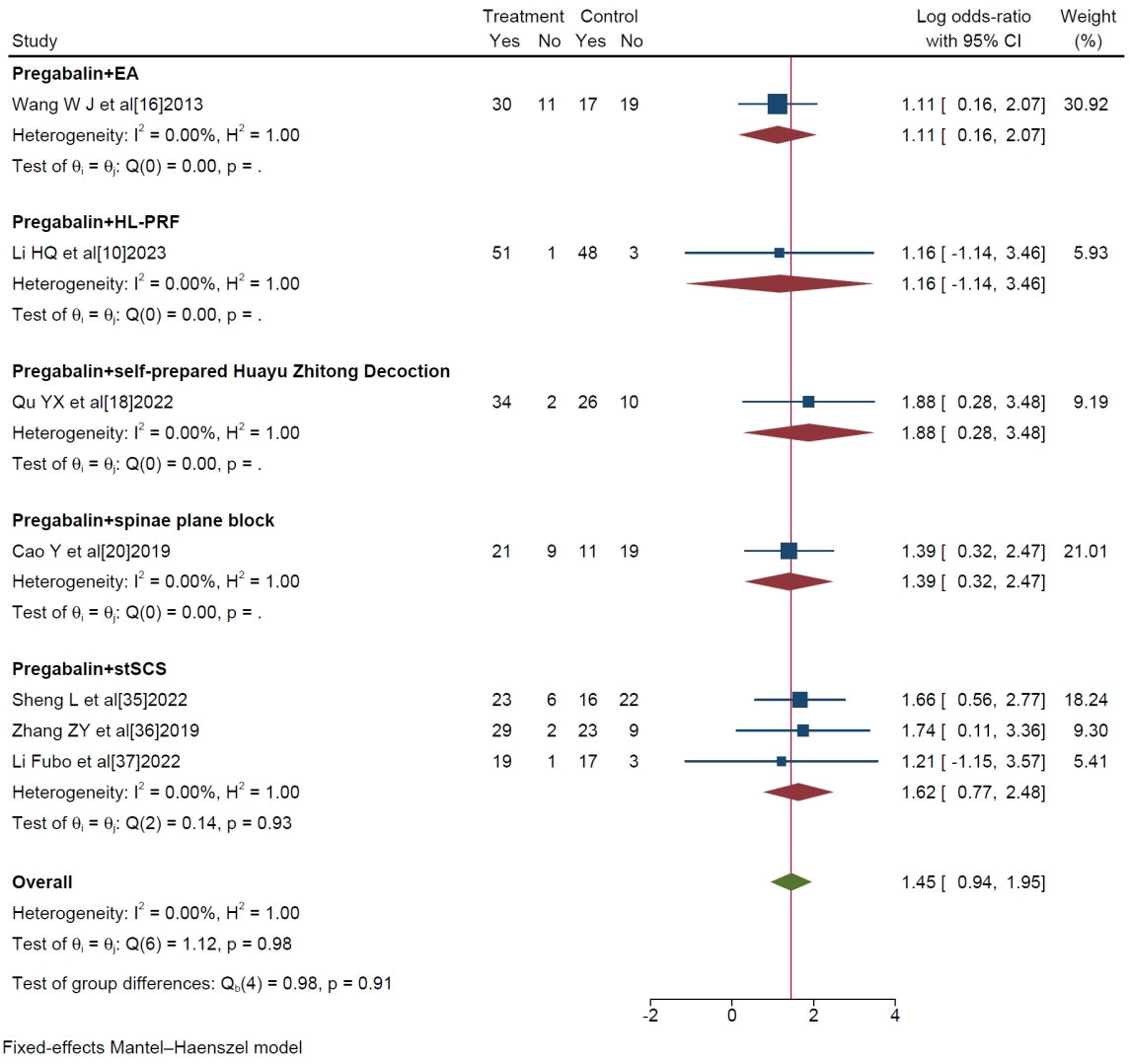

Figure 8. Meta-analysis of efficacy.

ed using the number of adverse reactions as a dichotomous variable. No significant heterogeneity was observed among the study results ($P > 0.1$, $I^2 < 50\%$), so a fixed-effect model was used for analysis. The results confirmed that there was no significant difference in adverse reactions between the intervention group and the control group (OR = 0.31, 95% CI: -0.01 to 0.62, Z = 1.92, P = 0.06). The 'Pregabalin + stSCS' subgroup had significantly fewer adverse reactions compared to the control group ($P < 0.05$). However, there were no significant differences in adverse reactions between the control group and the subgroups 'Pregabalin + EA', 'Pregabalin + HL-PRF', 'Pregabalin + Nerve block', 'Pregabalin + PNS', 'Pregabalin + PRF', 'Pregabalin + Sertraline', 'Pregabalin + lidocaine medicated plaster', 'Pregabalin + prednisone', 'Pregabalin + self-prepared Huayu Zhitong Decoction', and 'Pregabalin + spinae plane block' (all $P > 0.05$), as shown in **Figure 9**.

Meta-analysis of quality of life: Ten articles [12, 15, 22, 24-26, 31-33, 35] reported on quality of life, including 20 groups and 1,034 patients. A meta-analysis was conducted using quality of life scores as a continuous variable. There

Meta-analysis of pregabalin in the treatment of postherpetic neuralgia

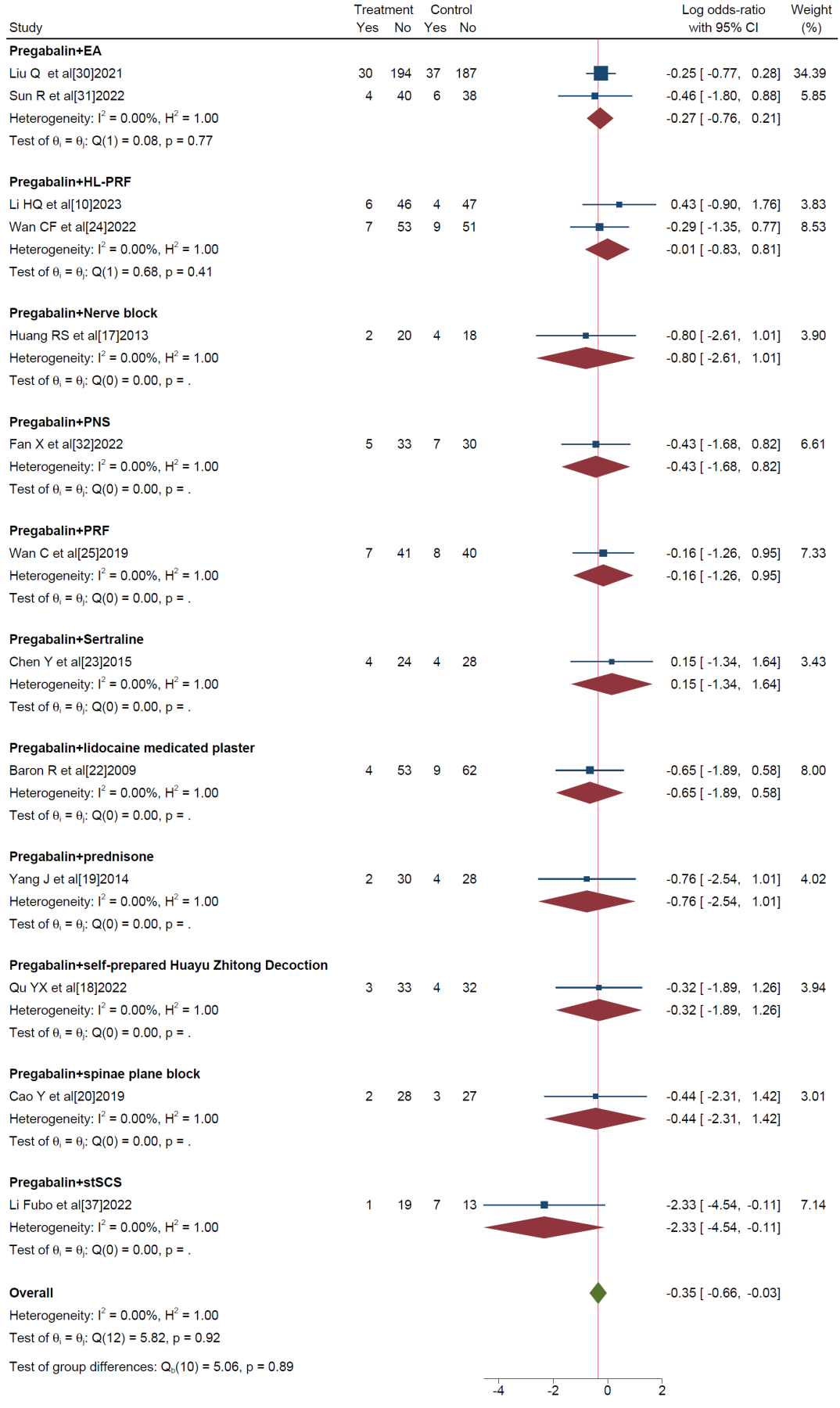

Figure 9. Meta-analysis of adverse reactions.

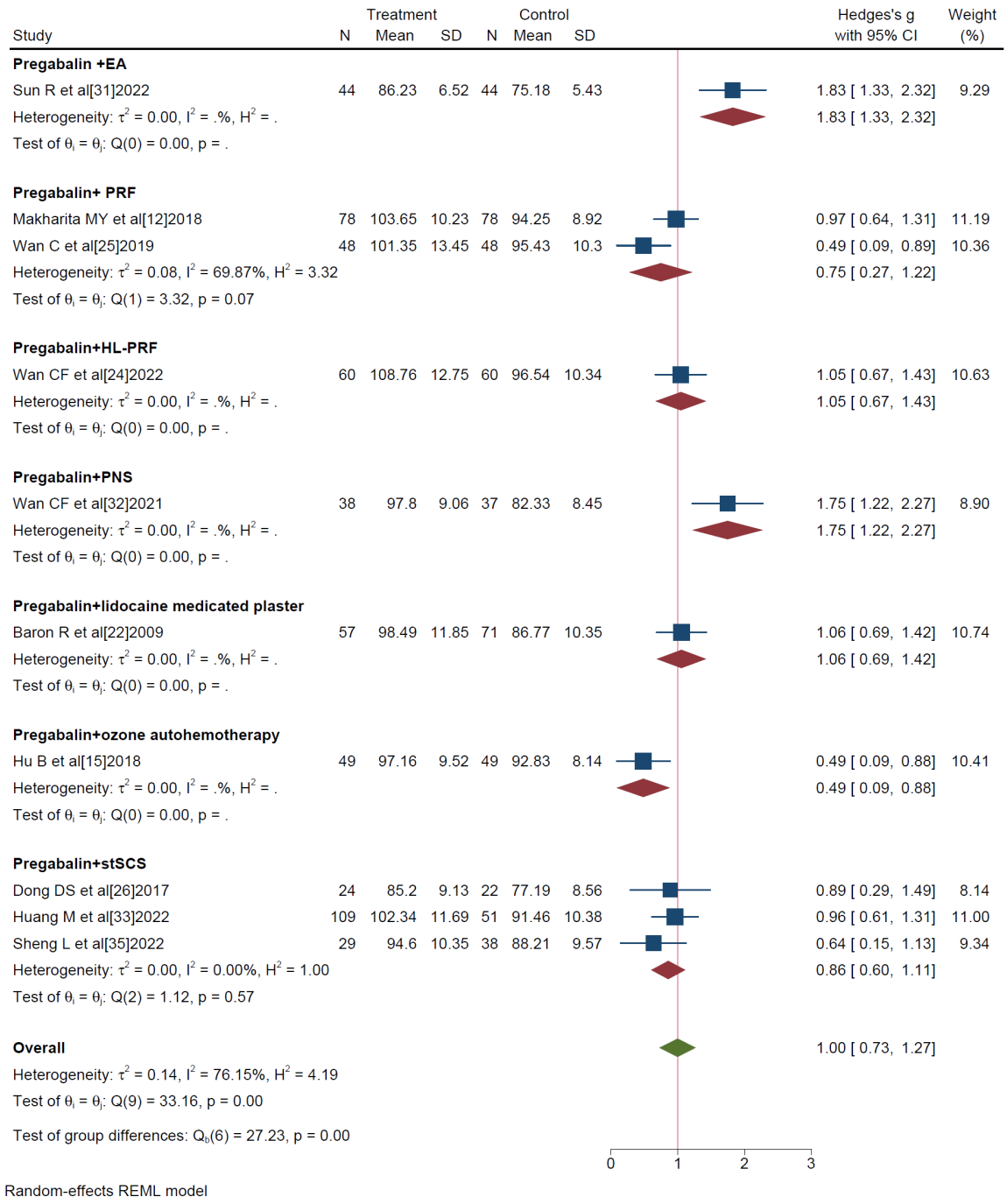

Figure 10. Meta-analysis of quality of Life.

was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the quality of life scores in the intervention group were significantly higher than those in the control group (OR = 1.00, 95% CI: 0.73 to 1.27, Z = 7.20, P < 0.01). Subgroups such as 'Pregabalin + EA', 'Pregabalin + PRF', and 'Pregabalin + HL-PRF' all had significantly higher quality of life scores compared to the control group (all P < 0.05), as shown in **Figure 10**.

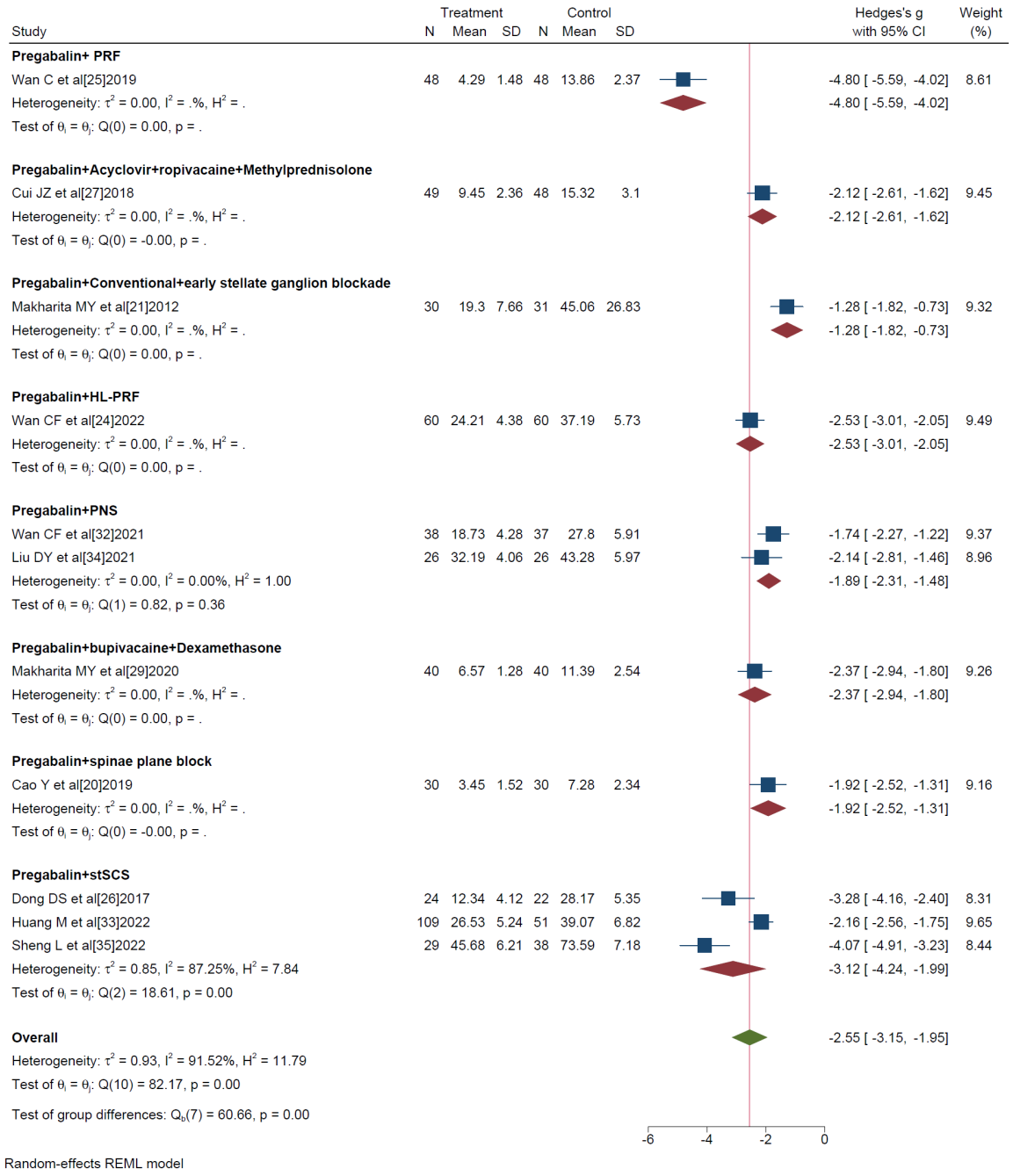

Figure 11. Meta-analysis of pregabalin dosage.

Meta-analysis of pregabalin dosage: Eleven articles [20, 21, 24-27, 29, 32-35] reported on pregabalin dosage, including 22 groups and 914 patients. A meta-analysis was conducted using pregabalin dosage as a continuous variable. There was significant heterogeneity among the study results ($P \leq 0.1$, $I^2 > 50\%$), so a random-effects model was used for analysis. The results confirmed that the pregabalin dosage in the intervention group was significantly lower than that in the control group (OR = -2.55, 95% CI: -3.15 to -1.95, Z = -8.30, $P < 0.01$). Subgroups such as 'Pregabalin + PRF', 'Pregabalin + Acyclovir + ropivacaine + Methylprednisolone', and six others all had significantly lower pregabalin dosages compared to the control group (all $P < 0.01$), as shown in **Figure 11**.

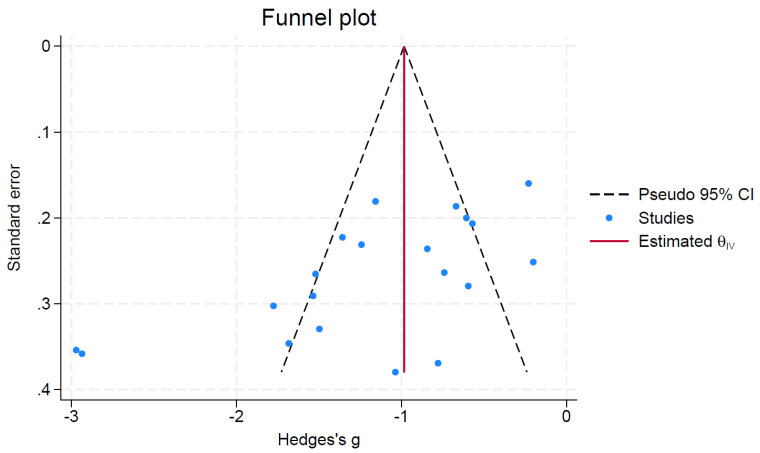

Figure 12. Funnel plot of VAS.

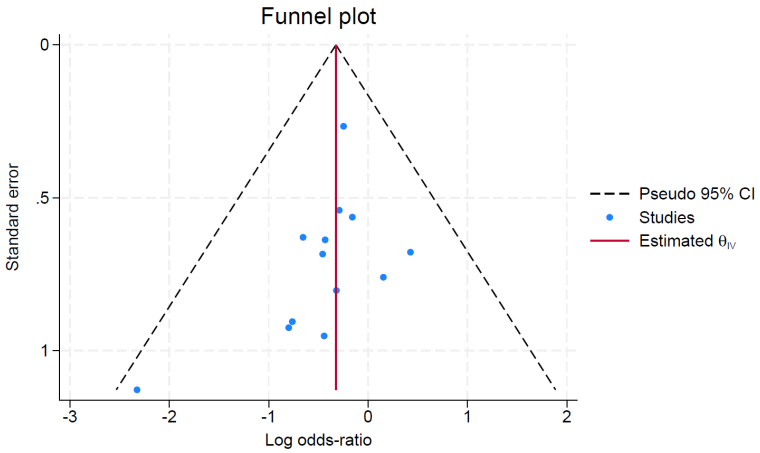

Figure 13. Funnel plot of adverse reactions.

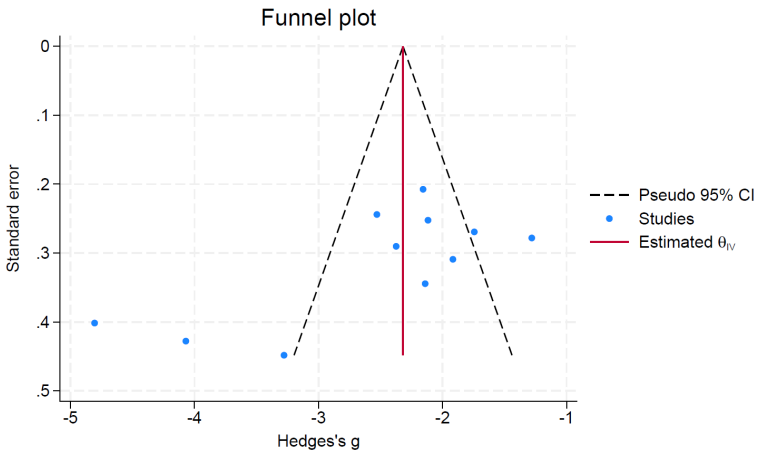

Figure 14. Funnel plot of pregabalin dosage.

Other indicators: The number of studies on indicators ⑥ and ⑩ is relatively small, and the combination is not meaningful, so no comparative analysis is performed.

Publication bias analysis

In the funnel plots for VAS and pregabalin dosage, some studies fall outside the 95% CI on both sides of the combined effect size dashed line, indicating publication bias. This may be related to factors such as medication and sample size (**Figures 12** and **14**). In the adverse reactions funnel plot, the studies are asymmetrically distributed on both sides of the combined effect size dashed line, with most studies close to the combined effect size, indicating no publication bias (**Figure 13**).

Discussion

The efficacy of combining pregabalin with various treatments for PHN

Pregabalin, as a first-line medication for treating PHN, primarily reduces pain by blocking gamma-aminobutyric acid (GABA) receptors and also has anti-anxiety and anti-epileptic effects. It is often used in combination with lidocaine patches, oxycodone, and other medications, but its efficacy can be affected by adverse reactions and tolerance doses. While traditional Chinese medical therapies like electroacupuncture and osteopathy show great potential for long-term pain control, they are mainly targeted at refractory PHN [38, 39]. Thus, selecting the right combination therapy remains a challenge in treating PHN. This study conducted meta-analyses on NRS and breakthrough pain, confirming the significant value of combinations such as “Pregabalin

+ EA", "Pregabalin + PNS", and "Pregabalin + stSCS" in reducing pain intensity and frequency. Additionally, reports on SF-MPQ, sleep quality scores, and VAS revealed that combinations like "Pregabalin + TENS" and "Pregabalin + oxycodone" can effectively lower pain scores in PHN patients. This can be attributed to the following reasons [40-42]: (1) Patient-controlled intravenous analgesia with hydromorphone can improve sleep quality and enhance pain relief for moderate to severe pain; (2) Prednisone can reduce capillary and cell membrane permeability, decrease inflammatory exudation, and inhibit the secretion and release of histamine and other toxic substances, thereby alleviating neural sensitivity and enhancing immune system function; (3) stSCS has several advantages, including being minimally invasive, having high safety, and rapid onset, and can promote nerve function recovery and regulate pain thresholds; (4) TENS can stimulate nerve fibers with specific electrical frequencies, closing pain gates within the spinal cord, promoting local circulation, and reducing muscle spasms and pain intensity.

Chen J et al. [43] found that the combination of PRF and pregabalin is significantly more effective than either pulsed radiofrequency alone or monotherapy. Traditional Chinese medicine (TCM) posits that PHN is caused by internal heat toxin and liver qi stagnation, leading to blood stasis and meridian obstruction. Prolonged development of these conditions can result in dysfunction of the five organs, malnutrition of the skin, and meridian spasms, causing a range of symptoms [44]. Electroacupuncture (EA) at specific acupoints, such as the Jiaji point, Neiguan point, and Baihui point, can promote blood circulation, relieve liver qi stagnation, and enhance nerve and fluid regulation through the conduction response of acupuncture, thus reducing the impact of pain on the body [45]. Therefore, although all combination regimens of pregabalin for the treatment of PHN are effective, physical stimulation such as TENS, stSCS, and PRF has the best advantages. At the same time, in response to the psychological problems caused by PHN, TENS, stSCS, PRF, etc. can also regulate the patient's autonomic nervous function, thereby improving their anxiety and depression, and improving their quality of life, social and psychological functions [46]. Reference [27] pointed out that pregabalin treatment in the early stage of herpes zoster pain, combined with antiviral drugs and other analgesics, can effectively shorten the duration of pain, reduce pain intensity and the occurrence of PHN. This suggests that preventive treatment of PHN can be carried out according to the condition of herpes zoster patients to reduce the incidence of PHN or control the progression of the disease.

The safety of combining pregabalin with various treatments for PHN

Cao X et al. [47] conducted a meta-analysis of 14 RCTs and found that pregabalin was significantly more effective than gabapentin, particularly in improving pain and sleep quality. However, it was also noted that pregabalin had significantly more adverse events compared to gabapentin. Ogawa S et al. [48] found that pregabalin can cause dizziness and drowsiness in PHN patients at the beginning of treatment. After the disease enters the stable stage, a small number of patients will also experience limb edema and weight gain. This analysis is related to the use of medication alone. Especially for patients with intractable pain, the effects of such analgesics and anticonvulsants are still limited. This requires us to consider the potential risks of combined medication in clinical practice. Pulsed radiofrequency (PRF) not only targets nerve root points for precise point-to-point repair of damaged tissue but also improves signal transmission between nerves, inhibits viral activity, and thus helps control symptoms and regulate local sensory and motor functions [48]. On the other hand, combining pulsed radiofrequency with pregabalin for PHN treatment can downregulate the expression of signal transduction genes PKA, PKC, and ERK, thereby reducing the stimulation of VZV by inflammatory mediators and oxidants, decreasing the release of pain factors, and reducing the incidence or recurrence of the disease [49]. However, in the subgroup analysis of adverse reactions, we found that, except for "Pregabalin + stSCS" which had significantly fewer adverse events than the control group, there were no significant differences in adverse reactions between the other subgroups, such as "Pregabalin + EA", "Pregabalin + HL-PRF", "Pregabalin + Nerve block", "Pregabalin + PNS", and "Pregabalin + PRF", and the control group.

This is because stSCS can cause higher-order centers to inhibit descending pathways, thereby cutting off the conduction of pain information [50, 51]. Moreover, short-term stimulation is safer and more tolerable, and can be adjusted in real time according to the patient's feelings, continuously improving abnormal symptoms of skin sensation and nervous system, and promoting early recovery of patients [52]. However, the treatment durations for PHN in various studies differ, such as 8 weeks for "Pregabalin + self-prepared Huayu Zhitong Decoction", 9 weeks for "Pregabalin + prednisone", and 4 weeks for "Pregabalin + HL-PRF". For patients with more complex conditions requiring long-term standardized treatment, the suitability of different combined therapies for long-term use and whether adverse reactions increase with prolonged treatment time need further investigation. Moreover, the occurrence of PHN is closely related to factors such as herpes zoster area, location, duration, endocrine metabolism levels, and age [53]. When evaluating adverse reactions of combined pregabalin treatments, it is necessary to consider the specific circumstances of PHN patients comprehensively.

The feasibility of combining pregabalin with various treatments for PHN

stSCS and PNS are both types of neurostimulation therapies and are commonly used alternatives to opioids and other analgesics. stSCS, when applied to the spinal cord nerves, can effectively inhibit the neurotoxic effects of herpes simplex virus, activate the spinal dorsal columns, and generate retrograde impulses that block or suppress anterograde pain impulses. On the other hand, PNS, when applied to peripheral nerves, can specifically alter electrical activities between neurons in different regions, promoting local nerve cell repair [54]. In the meta-analysis of pregabalin dosage, eight subgroups, including "Pregabalin + PNS" and "Pregabalin + stSCS", showed lower pregabalin dosages than the control group, indicating that combining pregabalin with other treatments is highly feasible. This can significantly reduce the incidence of adverse reactions and, at the same time, improve the safety of pregabalin while ensuring its efficacy. Furthermore, the combined methods used in the included studies each have their advantages. For example, study [17] conducted paravertebral nerve blocks under the guidance of a peripheral nerve stimulator, with pregabalin administered on the same day as the block. Study [20] investigated ultrasound-guided erector spinae muscle blocks combined with pregabalin. Study [29] used multiple local anesthetics for repeated paravertebral blocks on the basis of pregabalin. All three nerve block methods combined with pregabalin achieved relatively satisfactory results for treating PHN. Additionally, a systematic review and meta-analysis [55] indicated that continuous or repeated epidural anesthesia can also provide good analgesic or preventive effects for PHN. However, Kim JY et al. [56] hold a different view, arguing that epidural blocks do not effectively prevent PHN in herpes zoster patients and are not suitable for long-term use. Combining pulsed radiofrequency with analgesics is a clinically accepted method for treating neuropathic pain, but there is still a lack of objective and standardized evidence regarding the treatment dosage and efficacy of pulsed radiofrequency. Particularly for elderly and frail patients, combining pregabalin with nerve blocks or pulsed radiofrequency may increase psychological and economic burdens, affecting clinical treatment [57, 58]. Therefore, for patients who are not suitable for nerve blocks or pulsed radiofrequency treatments, other options such as combining pregabalin with EA, traditional Chinese medicine, or sertraline may be considered based on examination results and patient preferences.

Conclusion

Combining pregabalin with treatments such as electroacupuncture, medication, pulsed radiofrequency, and electrical nerve stimulation for PHN can achieve high levels of safety, effectiveness, and feasibility. The specific treatment approach should be selected based on individual circumstances. However, the occurrence of PHN is influenced by various factors, such as whether the condition is in the acute or stable phase and the presence of chronic diseases, which can affect the dosage of pregabalin and the outcomes of combination therapies. This article does not analyze these aspects, and the depth of research is still insufficient. Future studies should focus on a detailed clinical investigation of the safe dosages and long-

term efficacy of pregabalin combined with other treatments.

Disclosure of conflict of interest

None.

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